# Therapy of Osteoarthritis

Subjects: Others
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Osteoarthritis (OA) is a complex, multifactorial degenerative disease of the joint, characterized by chronic inflammation, progressive loss of articular cartilage, subchondral bone sclerosis and osteophyte formation, changes in the synovial membrane and increased volume of synovial fluid with altered coefficient of friction. In some respects, it can also be viewed as an inflammatory disease, leading to chronic pain and decrease of life quality.

Keywords: liposomes ; osteoarthritis ; intra-articular ; polysaccharides ; polyphenols ; anti-inflammatory activity

## 1. Overview

Osteoarthritis (OA) is a degenerative joint disease. An objective of the nanomedicine and drug delivery systems field is to design suitable pharmaceutical nanocarriers with controllable properties for drug delivery and site-specific targeting, in order to achieve greater efficacy and minimal toxicity, compared to the conventional drugs. The aim of this review is to present recent data on natural bioactive compounds with anti-inflammatory properties and efficacy in the treatment of OA, their formulation in lipid nanostructured carriers, mainly liposomes, as controlled release systems and the possibility to be intra-articularly (IA) administered. The literature regarding glycosaminoglycans, proteins, polyphenols and their ability to modify the cell response and mechanisms of action in different models of inflammation are reviewed. The advantages and limits of using lipid nanoformulations as drug delivery systems in OA treatment and the suitable route of administration are also discussed. Liposomes containing glycosaminoglycans presented good biocompatibility, lack of immune system activation, targeted delivery of bioactive compounds to the site of action, protection and efficiency of the encapsulated material, and prolonged duration of action, being highly recommended as controlled delivery systems in OA therapy through IA administration. Lipid nanoformulations of polyphenols were tested both in vivo and in vitro models that mimic OA conditions after IA or other routes of administration, recommending their clinical application.

## 2. Osteoarthritis

Osteoarthritis (OA) is a complex, multifactorial degenerative disease of the joint, characterized by chronic inflammation, progressive loss of articular cartilage, subchondral bone sclerosis and osteophyte formation, changes in the synovial membrane and increased volume of synovial fluid with altered coefficient of friction [1][2][3][4][5][6]. In some respects, it can also be viewed as an inflammatory disease, leading to chronic pain and decrease of life quality [5][7][8]. During OA progression, the degradation process of the collagen network takes place constantly and a variety of inflammatory mediators are detected in the articular cartilage. Tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β) influence chondrocyte metabolism, and also induce the production of inflammatory mediators, such as nitric oxide (NO), and prostaglandin E2 [9]. In these conditions, cartilage is further degraded and the inflammatory process is perpetuated [1][10][11]. Several studies indicated that local joint inflammation (synovitis) induced by endogenous molecular products derived from cellular stress and extracellular matrix degradation acted through innate inflammatory network and could influence the integrity and function of articular cartilage [12][13]. On the other hand, the systemic inflammation resulting from metabolic disturbance could also contribute to OA progression [13][14]. Some reports presented OA as a systemic disease and described the complexity of the involved inflammatory mechanisms [15]. Currently, there are no efficient treatments that can stop the pathological processes involved in OA progression, but prevention strategies and treatments directed to symptoms, pain relieve and function regain [16][17]. Treatments are based on various pharmacologic agents, such as selective cyclooxygenase-2 (COX-2) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, even analgesics [18]. Their administration through oral route involves limited bioavailability and risk of side effects, such as upper gastrointestinal and cardiovascular complications [19]. As OA has a localized nature, intra-articular (IA) administration of drugs provides the opportunity to improve the treatment by local depot formation and prolonged drug action [13][20][21][22][23][24]. Although numerous disease-modifying OA drugs (DMOADs) showed promising results in preclinical trials, their poor IA bioavailability limited the treatment approval [25]. In the last years, natural bioactive molecules (e.g., glycosaminoglycans (GAGs) from animal sources or plant polyphenols) have gained considerable

interest as therapeutic alternatives [19][26][27][28][29][30][31][32][33][34][35]. However, the efficacy of different anti-inflammatory bioactive molecules administration is limited due to their poor stability in the harmful biological milieu or low solubility, which decreases their bioavailability. Several delivery systems, including liposomes, microparticles, nanoparticles and hydrogels have been investigated for the sustained delivery and controlled release of bioactive molecules in the joints [5][36][37]. In vitro studies have demonstrated that in the case of OA, the phospholipidic layer acting as a boundary lubricant was missing from the articular surface of osteoarthritic degenerated cartilage and the structure of chondroitin sulfate (CS) was also changed [6]. Liposomes are the most commonly used nanocarriers to deliver drugs to human tissues in clinical applications and have been approved by the US Food and Drug Administration (FDA) [38]**.** As drug carrier systems, liposomes possess many biophysical and physicochemical properties suitable for IA administration, such as sustained release, ability for self-assembly and capacity to load large quantities of drugs [23][37]. Additionally, due to their ability to incorporate hydrophilic and hydrophobic molecules, good biocompatibility, low toxicity, activation and targeted delivery of bioactive compounds to the site of action, liposomes offer many advantages, such as the protection and efficiency of encapsulated material, solubilization of lipophilic molecules, prolongation of the duration of action and present targeting options. The clinical development of liposome-based drug delivery systems with synergistic therapeutic effect and a description of the technologies for NSAIDs liposomal formulations for orthopedic field applications were previously reviewed [39][40][41][42]. The only product approved in Germany and available on the market for IA administration in human patients with OA is Lipotalon®, containing the liposomal formulation of dexamethasone-21-palmitate [43].

## 3. Conclusions

Over recent years, delivery systems of biologically active compounds have become more advanced and complex when designing their lipid nanoformulation. Current research activities point towards finding an optimal formulation with suitable properties, capable of delivering encapsulated compounds. Liposomes have shown many advantages as carriers, including increased stability, reduced degradation, enhanced solubility of the drug, and improved pharmacokinetics. Several types of lipid nanocarriers have been developed for the treatment of different diseases, including OA, with increased attention being given to improve the delivery, efficacy, and safety. As we described in this review, lipid nanoformulations, mainly liposomes, loaded with natural bioactive molecules with anti-inflammatory activity, such as polysaccharides, polyphenols and proteins showed increased solubility and bioavailability, being able to improve their therapeutic effect in vivo. These are important aspects for further clinical research and the application of lipid nanoformulations for the treatment of OA.

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